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Tod R. Smeal

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08/08/2006

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EXAMINER

AEDER, SEAN E

ART UNIT

PAPER NUMBER

1642

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|---|-------------------------------------|--|
| Office Action Summary | Application No. 10/716,936 | Applicant(s) SMEAL ET AL. | |
| | Examiner Sean E. Aeder, Ph.D. | Art Unit 1642 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 June 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-15 and 18-25 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-15 and 18-25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Detailed Action

The Amendments and Remarks filed 6/9/06 in response to the Office Action of 1/11/06 are acknowledged and have been entered.

Claims 1-62 were pending.

Claims 26-62 were withdrawn from further consideration for being drawn to a non-elected invention (37 CFR 1.142(b)).

Claims 16-17 have been cancelled by Applicant.

Claims 1, 6, 15, and 18-20 have been amended by Applicant.

Claims 1-15 and 18-25 are currently under examination.

The text of those sections of Title 35 U.S.C. code not included in this Office Action can be found in a prior Office Action.

Specification

The objections to the specification are withdrawn in view of amendments.

Drawings

The objections to the drawings are withdrawn in view of amendments.

Rejections Withdrawn

The rejections of claim 1-25 under 35 U.S.C. 112, second paragraph, for being indefinite for failing to particularly point out and distinctly claim the subject matter which

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Applicant regards as the invention, are withdrawn in view of amendments and arguments.

Response to Arguments

Claims 1-15 and 18-25 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons of record in the Office Action of 1/11/06 and the reasons set-forth below. While being enabling for a method of detecting “an effect of the therapeutic composition on the mammal” wherein said effect is a decrease (or increase) in PAK4 phosphorylation on ser-474, the specification does not reasonably provide enablement for a method of detecting any other effect of a therapeutic composition on a mammal by measuring just any PAK4 phosphorylation. Further, while being enabling for a method of detecting differences in PAK4 phosphorylation on ser-474 by comparing two levels of phosphorylation of PAK4 on ser-474, the specification does not reasonably provide enablement for detecting differences in *every type of PAK4 phosphorylation* by comparing two levels of phosphorylation of PAK4 on ser-474. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Office Action of 1/11/06 contains the following text:

“The claims are drawn to a method of monitoring the effect of a therapeutic composition comprising measuring “a first PAK phosphorylation level” in a biopsy before administration of said composition, measuring “a second PAK phosphorylation level” in a biopsy after administration of said composition, and comparing the two

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phosphorylation levels to determine "an effect of the therapeutic composition" on a mammal. As broadly claimed, "a PAK phosphorylation level" encompasses changes in phosphorylation levels on *any* amino acid residue of *any* PAK family member, including those residues not involved in a family member's activation. Further, as broadly claimed, the claims encompass methods for monitoring a therapeutic involving biopsies from *any* mammal; including those without disease (see claim 1).

The specification teaches a phosphospecific anti-PAK4 polyclonal antibody, #108, which was raised against a fragment of PAK4 that was phosphorylated on serine-474 (paragraph 52, in particular). The specification further states that phosphospecific antibodies directed against serine-474 detect activated PAK4 (paragraph 4). The specification further states that "The data for the phosphospecific antibody (#108) in colon carcinomas is especially informative (6 out of 6 patients showed marked perinuclear staining in tumor and not distal benign tissue....This result strongly suggests that PAK4 is specifically active in colon tumor cells and inactive in benign colon tissue from the same patient. Staining of phosphorylated PAK4 was also observed in renal cell carcinoma, lung adenocarcinoma, prostatic adenocarcinoma, intraductal breast adenocarcinoma, and ovarian adenocarcinoma" (paragraph 80). The specification further states: "In tumors, strong staining with phosphospecific-PAK4 antibody was identified in colonic adenocarcinomas (while distal benign tissue failed to show phospho-PAK4 staining). On a scale of 0-3; "0" indicates no staining, "1" is indicative of weak staining, "2" indicates moderate staining and "3" indicates strong staining. Adenomatous epithelium was faintly to moderately positive, but most normal epithelium

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showed only staining of "1" for phosphorylated PAK4. Prostatic adenocarcinoma showed moderate staining ("2") (paragraph 81). The specification further states: "In benign tissues, the most prominent staining for phosphorylated PAK4 was seen in adipocytes, cardiac myocytes, sebaceous glands, and occasional macrophages. Additional positive cell and tissue types included hair follicles, benign prostatic epithelium, breast epithelium, and urothelium" (paragraph 82).

Though the data are not explicitly shown, the specification suggests that phosphorylation of PAK4 on ser-474 is indicative of colon carcinoma, where phosphorylation of PAK4 is described as being found in tumor and not in distal benign tissue (paragraph 80, in particular). However, the disclosure that breast epithelium stains positively for phosphorylated PAK4 indicates that the claimed method would not work with *the elected invention* of breast cancer. Further, the specification provides **no working examples** of the claimed invention, thus it is unclear whether a decrease in PAK4 phosphorylation would result in any kind of *therapeutic effect*. The specification only provides general guidelines or prophetic teaching of how changes in PAK phosphorylation levels could be used to monitor an undisclosed effect of a therapeutic composition (paragraph 9, in particular).

As evidenced by Qu et al (Molecular and Cellular Biology, May 2001, 21(10):3523-3533), PAK4 differs from other members of the PAK family in both sequence and function. For instance, PAK4 lacks several key features characteristic of PAKs 1, 2, and 3, including four proline-rich motifs, an autoinhibitory domain, and a putative G $\beta\gamma$ binding site (page 3524 left column, in particular). Further, "Unlike the

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other PAKs, Pak4 interacts with the effector loop mutant Cdc42C40" (page 3524 left column). Further, Qu et al states: "In contrast to other PAKs, we have found that activated PAK4 confers anchorage-independent growth on fibroblasts and leads to focus formation on soft agar assays" (page 3532 left column, in particular). Therefore, one of skill in the art would not reasonably assume that phosphorylation of PAK4 on ser-474 is indicative of activation, or phosphorylation, of any other PAK family member.

Colon carcinoma is the only ailment of which the disclosure demonstrates that PAK4 phosphorylation on ser-474 is indicative. If a molecule such as phosphorylated PAK4 is to be used as a surrogate for a diseased state, some disease state must be identified in some way with the molecule. There must be some phosphorylation pattern that would allow the claimed phosphorylated polypeptide to be used in a diagnostic manner. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation

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of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Due to the unpredictability of the art, one of skill in the art would only predictably be able to use PAK4 phosphorylated on residue Ser-474, but not any other PAK family member or any other phosphorylated residue of PAK4, in a diagnostic setting for colon carcinoma.

In view of the teachings above, and the lack of guidance or exemplification in the specification, it would not be predictable that the method would function as broadly contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the invention as broadly claimed. For the reasons above, Applicant only appears to be enabled for a method for monitoring the effect of a therapeutic composition on a mammal that has colon cancer, comprising measuring a first phosphorylation level of PAK4 on ser-474 before administration of a therapeutic composition to said mammal, and measuring a second phosphorylation level of PAK4 on ser-474 in a subsequent biopsy obtained from said mammal after administration of the therapeutic composition, wherein a lower level of PAK phosphorylation on ser-474 in

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the subsequent biopsy compared to the first biopsy indicates that the therapeutic composition decreases PAK4 activation."

In response to the Office Action of 1/11/06, Applicant has amended claims 1, 6, 15, and 18-20. Further, Applicant states: "According to the Examiner, the claims are enabled "for a method of monitoring the effect of a therapeutic composition on a mammal that has colon cancer, comprising measuring a first phosphorylation level of PAK4 on ser-474" before and after administration of the therapeutic composition".

The amendments to the claims and the Response filed 6/9/06 have been carefully considered, but are not deemed persuasive. The pending claims remain drawn to a method of detecting just any phosphorylation of PAK4 by measuring phosphorylation of PAK4 on ser-474 (see claim 1, in particular). Further, the pending claims remain drawn to a method of detecting any type of effect of the therapeutic composition on a mammal (see claim 1, in particular).

In regards to the pending claims remaining drawn to a method of detecting just any phosphorylation of PAK4 by measuring phosphorylation of PAK4 on ser-474, it is noted that claim 1 has been amended to twice recite "measuring...PAK4 on ser-474 phosphorylation level"; however, the claim further recites "...wherein a lower level of PAK4 phosphorylation..." (see claim 1). While being enabling for a method of detecting differences in PAK4 phosphorylation on ser-474 by comparing two levels of phosphorylation of PAK4 on ser-474, the specification does not reasonably provide enablement for detecting differences in every type of PAK4 phosphorylation by comparing two levels of phosphorylation of PAK4 on ser-474. One of skill in the art

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would recognize that a comparison between two levels of phosphorylation of PAK4 on ser-474 would indicate differences of PAK4 phosphorylation on ser-474 and not every other type of PAK4 phosphorylation.

In regards to the pending claims remaining drawn to a method of detecting just any type of effect of the therapeutic composition on a mammal, as noted in the Office Action of 1/11/06, while being enabling for a method of detecting "an effect of the therapeutic composition on the mammal" wherein said effect is a decrease (or increase) in PAK4 phosphorylation on ser-474, the specification does not reasonably provide enablement for a method of detecting any other effect of a therapeutic composition on a mammal by measuring just any PAK4 phosphorylation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Applicant is only enabled for a method of detecting "an effect of the therapeutic composition on the mammal" wherein said effect is a decrease (or increase) in PAK4 phosphorylation on ser-474. Applicant has not provided any evidence demonstrating that a decrease in PAK4 phosphorylation on ser-474 following administration of *anything* would be indicative of *any* other effect. Further, the specification provides no working examples of the claimed invention, thus it is unclear whether a decrease in PAK4 phosphorylation on ser-474 would result in any other effect, such as a *therapeutic effect*. The specification only provides general guidelines or prophetic teaching of how changes in PAK phosphorylation levels *could* be used to monitor an undisclosed effect of a therapeutic composition (paragraph 9, in particular).

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to a method of detecting changes in every type of PAK4 phosphorylation by comparing levels of PAK4 ser-474 phosphorylation, and Applicant has not enabled a method of detecting changes in every type of PAK4 phosphorylation by comparing levels of PAK4 ser-474 phosphorylation because it has not been shown that comparing levels of PAK ser-474 phosphorylation would predictably detect changes in every type of PAK4 phosphorylation. Further, the claims are broadly drawn to a method of detecting just any type of effect of the therapeutic composition on a mammal by comparing levels of PAK4 ser-474 phosphorylation, and Applicant has not enabled said method because it has not been shown that the method of comparing levels of PAK4 ser-474 recited in the claims would predictably determine every type of effect.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

Summary

No claim is allowed. Claims 1-15 and 18-25 are rejected under 35 U.S.C. 112, first paragraph, but free of the prior art teaching a method of monitoring an effect of a therapeutic comprising measuring PAK-4 ser-474 levels before and after administering said therapeutic. The closest prior art for claims 1-15 and 18-25 is Callow et al (The

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Journal of Biological Chemistry, 1/4/02, 277(1): 550-558), which teaches a requirement for PAK4 in the anchorage-independent growth of some human cancer cell lines; however, this reference does not teach or suggest a method of monitoring an effect of a therapeutic comprising measuring PAK-4 ser-474 levels before and after administering said therapeutic.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. ' 1.136(a). A shortened statutory period for response to this Final Action is set to expire three months from the date of this action. In the event a first response is filed within two months of the mailing date of this Final Action and the advisory action is not mailed until after the end of the three-month shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. '1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than six months from the date of this Final Action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SEA


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